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| 10/806,774 | 03/23/2004 | Achim H. Krotz | ISIS-5429 | 2386 |

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| EXAMINER | |
|---|---|
| CRANE, LAWRENCE E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1623 | |

DATE MAILED: 07/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/806,774 | KROTZ ET AL. | |
| | Examiner | Art Unit | |
| | L. E. Crane | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03/23/2004 (prelim amdt)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *42-128* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-128* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/30/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims **1-41** have been cancelled, no claims have been amended, the disclosure has been amended, and new claims **42-128** have been added as per the preliminary amendment filed March 23, 2004. An Information Disclosure Statement (IDS) filed April 30, 2004 has been received with all newly cited references and made of record.

Claims **42-128** remain in the case.

Claims **50 and 77** are objected to because of the following informalities:

In claim **50** the acronyms "DCA" and "TCA" have not been defined; e.g. -- dichloroacetic acid (DCA) -- and -- trichloroacetic acid (TCA) --.

In claim **77** at line 1, the term "detprotecting" is a misspelling of the term -- deprotecting -- .

Appropriate correction is required.

Claim **42** is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention; the scope is excessive in view of the disclosed exemplifications.

The term "arene solvent" in claim **42** is directed to a vast number of chemical compounds which have not been described in the instant disclosure in a manner permitting the ordinary practitioner to have the guidance necessary to use a very large proportion of the compounds encompassed in the process improvement claimed. Examiner finds only **benzene-ring-containing** compounds provided in the "Examples" section and none of these compounds includes either the unlimited variations substituents and unlimited variations of aromatic ring types allowed within the scope of the generic term "arene."

Claims **42, 44. 49, 51-52, 59, 74, 79, 84, 103, 110, 125 and 128** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims **42 and 51** the term "trityl group" appears to have two different meanings (generic and then specific). Examiner suggests that the first occurrence of the noted term in both claims should be replaced by the term -- protecting group --, -- trityl-type --, or the like in order to avoid confusion.

In claim **44** at line 2, the term "from about 1 to 4 phenyl groups" may be incorrect because the term being defined is "alkylbenzene." Did applicant intend the term to read -- from about 1 to 4 alkyl groups -- ? Alternatively, claim **44** lacks proper antecedent basis in claim **42** and the term -- further comprising -- should be introduced into claim **44**.

Claim **49** lacks proper antecedent basis in claim **42** because the reagent in the detritylation step, and therefore the specific type of detritylation process (acid hydrolysis, solvolysis, hydrogenolysis, etc.), has not been specified in claim **42**. Examiner suggests introduction of the term -- further comprising -- to overcome this grounds of rejection. Alternatively applicant may elect to expand the preamble of claim **42** to more completely describe the particular step or steps of an oligonucleotide synthesis or syntheses being improved. See also claims **74, 99 and 125** wherein the same error reoccurs.

In claim **51** at line 2, the term "or" is incorrect and by its presence raises questions concerning whether there is a valence error. Examiner suggests substitution of the term -- and -- therefore to make the Markush group complete, or elimination of the Markush preamble, as two possible routes to overcoming the instant rejection.

In claims **52, 59, 84, 103 and 110** the term "1,1-dianisyl-2,2,2-trichloroethyl (DATE)" is incomplete because the included term "anisyl," apparently referring to a substituent group derived from anisole (aka methoxybenzene), is missing a prefix specifying the point of attachment of the methoxyphenyl group as ortho, meta and/or para.

Claim **128** lacks proper antecedent basis in claim **103** because the noted claim includes subject matter not present in parent claim **103**. Examiner suggests introduction of the term -- further comprising -- into claim **128** as a solution to this problem. See also claim **102**.

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **42-128** are rejected under 35 U.S.C. §103(a) as being unpatentable over **Ravikumar '621** (PTO-892 ref. **A**) in view of **Caruthers et al. '679** (PTO-892 ref. **G**) and further in view of **Froehler et al. '076** (PTO-892 ref. **H**), **Horn et al.** (PTO-892 ref. **WA**), **Horn et al.** (PTO-892 ref. **UA**), **Sproat et al.(I)** (PTO-892 ref. **W**), **Conway et al.** (PTO-892 ref. **Y**), **Atkinson et al.** (PTO-892 ref. **Z**), and **Sproat et al.(II)** (PTO-892 ref. **RA**), and still further in view of **Perrin et al.** (PTO-892 ref. **XA**), **Aldrich Handbook/Catalog** (PTO-892 ref. **YA**) and **Greene et al.** (PTO-892 ref. **ZA**).

The instant claims are directed to entirely conventional, 7 step oligonucleotide syntheses conducted using an automated device to, wherein the variations from the prior art are
i) the limitation of the choice of solvent or solvent mixture present for 5'-O-deprotection to an "arene"-type solvent selected from the groups consisting of

a) an aromatic or alkyl aromatic solvent (e.g. benzene, naphthylene, azulene, toluene, a xylene, mesitylene, etc.);

b) a halogenated aromatic solvent (chlorobenzene, etc.);

c) a halogenated alkyl aromatic solvent (p-chlorotoluene, etc.); and

d) an aromatic ether solvent (anisole, diphenylether, etc.).

ii) the limitation of an optionally specified trityl-type protecting group to be removed in the deprotection step chosen from a maximum of up to 9 specific alternatives known protecting groups; and
iii) the optional limitation to a specified "protic acid" chosen from up to 9 specific alternatives as the reagent which causes detritylation.

**Ravikumar '621** (PTO-892 ref. **A**) discloses entirely conventional oligonucleotide synthesis wherein the solvent for the coupling step is acetonitrile in the examples and the P-protecting group varies from the conventional phosphorus-ester protecting group. At column 3

this reference refers to several different patents which disclose the solid phase synthesis of oligonucleotides including three Caruthers et al. patents now cited herein as PTO-892 references **I, J and K**. Each of these Caruthers et al. patents discloses the automation of the synthesis of oligonucleotides via process steps closely analogous to, if not identical with, the process steps claimed herein, the most detailed disclosure occurring in Caruthers et al. '418 (PTO-892 ref. **K**). In the **Ravikumar '621** patent at column 10, lines 1-16, a generic disclosure of the process steps leading to an oligonucleotide is presented, including acid-mediated deprotection of the 5'-hydroxyl moiety of a solid-support-attached nucleoside. However, no disclosure of any preferred solvent for the required acid reagent is included. In the same column at line 50, the removal of 5'-hydroxyl protection by contact with acid from a solid-support-attached oligonucleotide is also taught without specifying any particular solvent. At column 14, lines 5-28, a more complete disclosure of possible 5'-hydroxyl protecting groups is provides along with a list of acids effective to deprotect, but no preferred solvents are listed. At column 18, lines 37-41, deprotection is accomplished by contact with a solution of dichloroacetic acid in dichloromethane, conditions repeated in subsequent experimental procedures. The choice of any particular deprotection solvent is therefore apparently a choice within the purview of the ordinary practitioner in view of this disclosure. This reference does not disclose the particular mixture of solvents selected for application in the instant claimed processes.

**Caruthers et al. '679** (PTO-892 ref. **G**) at column 5, lines 10-14, teaches the use of "... any solvent which will dissolve the reactants ..." including a list of specific organic solvents for phosphoramidite-intermediate-based oligonucleotide synthesis. The context of this statement suggests that Caruthers was making reference to the coupling step. However, the same generic teaching appears to also apply to the deprotection step where four different solvent/reagent systems were disclosed by Caruthers as effective in the 5'-O-detritylation process:
(1) see column 16, Table IV, footnote 1 ($ZnBr_2$ in nitromethane);
(2) see column 16, Table V, footnote 1 (toluenesulfonic acid in chloroform:methanol (7:3));
(3) see column 18, lines 26-28 ($ZnBr_2$ in nitromethane:methanol (19:1)); and
(4) see column 19, lines 47-50 (80% acetic acid).
This reference does not disclose the particular mixture of solvents selected for application in the instant claimed processes.

**Froehler et al. '076** (PTO-892 ref. **H**) discloses the use of H-phosphonate intermediates for the coupling step in the synthesis of oligonucleotides and phosphorothioate analogues thereof, including reference to the automated synthesis thereof using a "Biosearch Model 8600 DNA synthesizer" at column 9, lines 22-23. This reference also teaches the use of " ... an anhydrous organic solvent, preferably pyridine/acetonitrile ...," at column 5, lines 26-28. This "whatever works best" philosophy apparently also applies to the deprotection step; see column 5, lines 38-47. The last line of this portion of column 5 is particularly instructive. After listing 3 (three) different deprotection reagent/solvent mixtures, **Froehler** suggests a very flexible "whatever works" approach by further stating that "[o]ther deprotection procedures suitable for other known protecting groups will be apparent to the ordinary practitioner." This reference does not disclose the particular mixture of solvents selected for application in the instant claimed processes.

**Horn et al.** (PTO-892 ref. **WA**) at page 6965, first complete paragraph (lines 19-28), discloses the use of dichloroacetic acid in toluene for the trityl deprotection step in the synthesis of branched oligonucleotides. Horn notes in particular that a higher than usual (for single deprotection) concentration of dichloroacetic acid effects rapid de-tritylation when multiple de-tritylations must be conducted simultaneously in the parallel extensions of separate oligonucleotide chains is required for the synthesis of multiply branched oligonucleotide "fork and comb" type probes. This reference does not disclose all of the particular combinations of solvents and reagents selected for application in the instant claimed processes.

**Horn et al.** (PTO-892 ref. **UA**) at page 4844, columns 1-2 (following the header "**Oligonucleotide synthesis**"), discloses further details relevant to the application of a mixture including dichloroacetic acid and toluene/methylenechloride to effect the de-tritylation of linear 5'-tritylated oligonucleotide precursors during the process of oligonucleotide chain extension. See particularly page 4844, column 2 at lines 6-8 and 25-28. This reference does not disclose all of the particular combinations of solvents and reagents selected for application in the instant claimed processes.

**Sproat et al. (I)** (PTO-892 ref. **W**) discloses at p. 52, (lines 2 and 18) that toluene is useful for the purification of synthetic nucleoside intermediates. Additionally, this reference discloses at pp. 64 (Protocol 17, step 3) and page 70 (Protocol 25, step 4) that benzene is a

solvent for key oligonucleotide synthesis reagents and for nucleoside-3'-O-phosphoramidites, and may be used to co-evaporate triethylamine therefrom.

**Conway et al.** (PTO-892 ref. **Y**) is directed to the chemical synthesis of labeled DNA and at p. 218, Section C, Subsection 2, discloses the specific use of toluene as an effective solvent for dissolution of pyridine-contaminated dinucleoside monophosphorothioate d[Cp(s)C] prior to co-evaporative removal of the pyridine/toluene mixture therefrom. The instant reference does not disclose that toluene is used in the coupling step required to make this compound.

**Atkinson et al.** (PTO-892 ref. **Z**) discloses at p. 43 in section (xvii), that toluene is useful to dissolve the 3'-O-phosphoramidites of 2'-deoxyadenosine, 2'-deoxycytidine, and 2'-deoxyuridine as the first step in a re-precipitation or recrystallization process. This reference also teaches at p. 76, section 7.5, "Variation in Procedures," although no specific teaching of the substitution of an aromatic solvent from other solvents used in oligonucleotide synthesis is present in this section. In section 8.7 at p. 80, "toluene" is listed as a reagent useful in the preparation of "Deoxyribonucleoside-derivatized supports." This reference at the noted locations does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

**Sproat et al.(II)** (PTO-892 ref. **RA**).at p. 84, lines 10 and 9 from the end of the page, discloses that the "[p]urity of solvents and reagents is of the utmost importance as far as reliability and reproducibility of the [oligonucleotide synthetic] method are concerned." This reference also discloses at p. 93, section (xv), that a di-protected adenosine derivative may be effectively dissolved in toluene prior to evaporative solvent removal for the purpose of co-evaporating residues of pyridine therefrom (see also p. 96, section (vi) for a similar disclosure). Additionally, at p. 111, section 7.6, the listing of solvents useful in oligonucleotide synthesis includes both benzene and toluene. This reference at the noted locations does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

**Perrin et al.** discloses a long list of organic compounds including a large number of aromatic solvents including examples which fit within each of the subgeneric groups defined

by the term "aromatic solvent," "alkyl aromatic solvent," "halogenated aromatic solvent," "halogenated alkyl aromatic solvent," "aromatic ether solvent." This reference also discloses how to purify each of the compounds listed. This reference does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

**Aldrich Catalog Handbook of Fine Chemicals** discloses a long list of organic compounds including a large number of aromatic solvents including examples which fit within each of the subgeneric groups defined by the term "aromatic solvent," "alkyl aromatic solvent," "halogenated aromatic solvent," "halogenated alkyl aromatic solvent," "aromatic ether solvent." The relevant examples are noted with checkmarks on the particular pages of the catalog made of record. This reference does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

**Greene et al.** (PTO-892 ref. **ZA**) discloses at pages 60-65 six different 5'-"trityl type protecting groups i) trityl, ii) monomethoxytrityl, iii) dimethoxytrityl, iv) trimethoxytrityl, v) 4.4',4"-tris(benzoyloxyphenyl)methyl and vi) 9(9-phenyl)xanthenyl, and at pages 61-62 discloses the following acids as effective cleavage reagents for protecting group removal: a) formic acid, acetic acid, trifluoroacetic acid, HCl, $SnCl_2$, $Et_2AlCl$, TsOH, boron trifluoride etherate and $ZnBr_2$.

The teachings of the prior art **Caruthers '679** and **Froehler '076** references motivate the selection of practically any organic solvent or solvent mixtures which will dissolve the reactants and not otherwise interfere with the intended synthetic transformation. The first three references (**A, G and H**) and the additional **Caruthers et al.** patents cited by **Ravikumar et al. '621** provide descriptions of conventional prior art processes for making oligonucleotides via phosphoramidite or H-phosphonate intermediates, including the 5'-O-deprotection process step and including details of how the process has been automated in reference **H** and by patents cited in reference **A**. The noted portions of the **Caruthers '679** and **Froehler '076** both teach that the choice of a particular solvent or solvent mixture is a variable clearly within the purview of the ordinary practitioner.

The **Horn et al.** references provide nearly exactly on point examples wherein an aromatic solvent or solvent mixture (toluene or toluene/methylene chloride) together with dichloroacetic acid are effective in the 5'-O-deprotection of oligonucleotides during the process of synthesis.

The **Sproat et al. (I) (W)**, **Conway et al.**, **Atkinson et al.**, and **Sproat et al. (II)(RA)** references are each generally directed to oligonucleotide synthesis thereby providing proper motivation to combine with the primary references. These secondary references provide disclosures that at least two different nucleoside-3'-O-phosphoramidites, at least one dinucleotide derivative, and some other nucleoside derivatives may be effectively dissolved in the aromatic hydrocarbon solvents benzene and/or toluene. These disclosures are deemed to provide factually specific motivations for the ordinary practitioner conducting routine experimentation to substitute toluene, benzene, or their closely related aromatic solvent relatives as substitutes for at least a portion of the solvents typically used during the deprotection step in oligonucleotide synthesis. The selection of "aromatic" solvents is vast as revealed by the very large number of alternatives (indicated with arrows) in **Perrin et al.** and the even larger number of commercially available alternatives listed (checked off )in the **Aldrich Catalog**. The selection of protecting groups disclosed in **Green et al.** along with acids suitable for removal thereof is considerable. And lastly, in light of the absence of any unexpected results, the choice of substrate (linear vs. branched oligonucleotide) is deemed to not be a basis for finding patentable distinction over the prior art of record. For these reasons the instant process claims are deemed to be lacking in any patentable distinction in view of the noted prior art.

Therefore, the instant claimed oligonucleotide processes would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Claims **42-128** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Horn et al.** (PTO-892 ref. **WA** in view of **Horn et al.** (PTO-892 ref. **UA**).

The subject matter of the instant claims is described in the previous rejection.

**Horn et al. (WA)** at page 6965, first complete paragraph (lines 19-28), discloses the use of dichloroacetic acid in toluene for the trityl deprotection step in the synthesis of branched

oligonucleotides. Horn notes in particular that a higher than usual (for single deprotection) concentration of dichloroacetic acid effects rapid de-tritylation when multiple de-tritylations must be conducted simultaneously in the parallel extensions of separate oligonucleotide chains is required for the synthesis of multiply branched oligonucleotide "fork and comb" type probes.

**Horn et al. (UA)** at page 4844, columns 1-2 (following the header "**Oligonucleotide synthesis**"), discloses further details relevant to the application of a mixture including dichloroacetic acid and toluene/methylenechloride to effect the de-tritylation of linear 5'-tritylated oligonucleotide precursors during the process of oligonucleotide chain extension. See particularly page 4844, column 2 at lines 6-8 and 25-28.

The prior disclosures of standard phosphoramidite-type oligonucleotide syntheses of either branched or linear oligonucleotides wherein the de-tritylation step relies on a mixture comprising dichloroacetic acid and toluene are deemed to be teachings which individually, or in combination, read on the instant claimed process. For this reasons the instant process claims are deemed to be lacking in any patentable distinction in view of the cited prior art.

Therefore, the instant claimed oligonucleotide processes would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F. 2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir 1985); and *In re Goodman,* 29 USPQ 2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.78(d).

Effective January 1, 1994, a registered attorney or agent or record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

Claims **42-128** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-42** of copending Application No. **09/032,972**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the improvements in the methods of making oligonucleotides are directed to substantially overlapping subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35 U.S.C. §103(a).

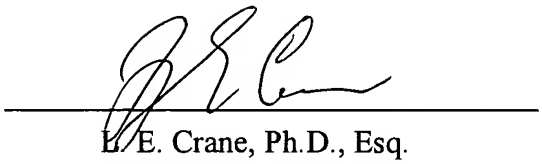
Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX (unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 703-872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **571-272-0661**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
**07/11/2005**



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